REMARKS

In the Office Action mailed January 10, 2006 Claims 18, 20, 22-28, 30-36, and 38-41 were pending for consideration in the present application. Each of these claims was rejected under 35 U.S.C. 103(a) as allegedly unpatentable over WO 99/40943 (hereinafter WO '943).

By the present amendment claim 18 has been amended so as to correct a typographical error in the previously presented claim. No new matter was added in the amendment. Additionally, it should be understood that such amendments are made solely for the purpose of expediting the prosecution of the present matter and without conceding the correctness of the present rejection.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 18, 21-28, 30-36, and 38 under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Examiner has rejected claim 18 as allegedly lacking clarity based on the phrase "if dissolution than pure unprocessed drug." Claim 18 has been amended so as to correct a typographical error, namely by amending the word "if" to the word "of." Applicants assert that such an amendment remedies any alleged lack of clarity. As such it is respectfully requested that this rejection be withdrawn.

The Examiner has also rejected claim 24 for allegedly lacking clarity. Specifically, the Examiner states that "claim 23 recites that the surfactant is an organic excipient. However claim 24, dependent from claim 23, sets forth a number of excipients including organic solvents, phosphates, non-crystalline cellulose etc., which are not emulsifiers by nature." The Applicants assert that the specification is sufficiently clear with regard to what can be used as a "surfactant" for the present invention. Specifically, the Examiner is directed to page 16, line 6 to page 17, line 2 of the original specification. The Examiner is also directed to page 20, lines 6-25 which states in part "in most cases, the surfactant will be an organic solvent." The Examiner is reminded that pursuant to MPEP § 2111.01 an Applicant may be his or her own lexicographer. Thus, even if, *arguendo*, the Examiner is correct in her statement that some of the compounds listed in the present application are not traditionally classified as surfactants, the clear teaching of such compounds as

surfactants in the specification under the present invention is sufficient to render the claims definite and without ambiguity. As such it is respectfully requested that the rejection be withdrawn.

Claims 18, 21-28, 30-36, and 38 were rejected by the Examiner under 35 U.S.C. §112, first paragraph as allegedly failing to adequately enable the claims. Specifically, the Examiner stated "the final outcome of the claimed method i.e., drug with improved solubility depends on several factor such as on the type or solubility of the drug, melting point of the surfactant, the high shear employed (such that cooling occurs properly), all of which are specific depending on the drug and surfactant and the eutectic mixture." The Applicants respectfully traverse the Examiners rejection. Each of the factors set forth by the Examiner will be discussed individually below.

With regard to drugs which can be used in the present invention, the specification clearly sets forth types and solubilities for such drugs. Specifically, the originally filed specification states that the drug substance "can be poorly or sparing soluble" meaning "that the drug substance has a solubility in a liquid dispersion medium of less than about 100 mg/ml, and preferably of less than about 1 mg/ml." Page 14, lines 5-11. Additionally, as noted by the Examiner, suitable classes of drugs are set forth beginning on page 14, line 19. Collectively these two portions of the specification provide more than ample guidance as to the types and solubility characteristics of drugs which can benefit from the present invention.

Regarding the types of surfactants which can be used, the specification clearly lists specific compounds which can be used. *See* page 16, line 6 to page 17, line 10. A list of particularly preferred surfactants is also set forth in the originally presented specification. Page 17, line 11 to page 18, line 2. Further description of characteristics of the surfactants can also be found in the originally filed specification. On page 18, lines 3-6, the specification states that the surfactants "do not chemically react with the drug substance or itself" and that the molecules of the surfactant are "essentially free of intermolecular crosslinkages." As noted by the Examiner in the Office Action, the specification also teaches that "the surfactant should have a melting point above about room temperature and preferably above about 40 °C." Page 19, lines 22-24. The specification further states that "the surfactant must be miscible with the drug." Page 20, lines 6-7. Together, these descriptions clearly provide one skilled

in the art with sufficient details in order to select a surfactant which could be used in the present invention.

The term "high shear" as used in the present invention is also clear in the originally filed specification. First, high shear is a common term well known in the pharmaceutical arts and, as such, would be readily understood by one of ordinary skill in the art. Although the specification does not expressly define high shear it states that "[t]here are a large variety of these [high shear devices] available on the market readily ascertainable by one of ordinary skill in the art for the intended purpose of the present invention." An example of what can constitute high shear is set forth in Example 1. The Example states that a mortar and pestle was used to "vigorously" grind the surfactant-drug mixture as it cooled. With these teachings in mind, one skilled in the art could readily surmise that the well known term "high shear" was intended to include, at the very least, vigorous mixing using a mortar and pestle. Other mechanical high shear devices, such as those known to those of ordinary skill in the art, are also acceptable for use.

Based on the clear teachings in the originally filed specification one of ordinary skill in the art would readily be able to determine which drugs and surfactants could be used in the present invention and the meaning of high shear. The Examiner seems to imply that dimenhydrinate is the only enabled drug because it is the only one which is paired with a specific surfactant. The Applicants respectfully disagree with such an implication. It is well within the skill of one in the art to determine compatibility of certain drugs with certain surfactants, especially when the drug and surfactant characteristics are defined as in this invention. The presently pending claims are not drawn to specific drug-surfactant combinations but rather drug and surfactant combinations which meet the characteristics set forth above, and which can be used together in a method for making micro- and nano-particulate drug compositions. As such the Applicants assert that the presently pending claims are adequately supported in the originally filed specification. Therefore, it is respectfully requested that the rejection be withdrawn.

The Present Invention

The method recited by the presently pending claims involves a process for preparing micro- and nano-particles of a drug coated with a surfactant. Such a

process generally includes the steps of melting an amount of the drug in a molten surfactant miscible with the drug to form a drug-surfactant mixture; heating the mixture to a temperature above the mixture's melting point but below the decomposition temperature of the drug, and to which a clear mixture is formed; and subsequently cooling the mixture to approximately room temperature while continuously mixing under high shear so as to maximize formation of drug particles coated with the surfactant. The goal of such process is to impart improved solubility to the drug particles, and in fact, Applicant's testing results as contained in the examples of the present specification show that the coated drug particles do in fact, have a greater rate of dissolution than pure unprocessed drug. It is noteworthy that the present invention, including the presently pending claims, requires that the drug be melted into a molten surfactant miscible with the drug to form a drug-surfactant mixture. Miscibility, by definition, describes "the ability of a liquid or gas to dissolve uniformly in another liquid or gas." *Hawleys Condensed Chemical Dictionary,* 13th Edition. The present invention requires that the surfactant be miscible with the drug, or in other words, when melted, the drug can be described as being dissolved in the surfactant.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 18, 20, and 22-38 under 35 U.S.C. 103(a) as allegedly being unpatentable over WO '943. The Applicants respectfully submit that these claims are patentable over the cited reference for the reasons set forth below, and that the rejection should be withdrawn.

While Applicants are confident in the Examiner's understanding of the elements required to establish a *prima facie* case of obviousness, Applicants would like to take this opportunity to briefly summarize this standard. Essentially, in order to establish a *prima facie* case of obvious, the Examiner must meet the burden of showing: 1) that the reference as modified or combined teaches or suggests all of the claim elements; 2) that there is sufficient motivation within the reference itself to make the modification or combination asserted; and 3) that such modification or combination is likely to be successful.

WO '943 teaches a delivery system and related process for enhancing the solubility of poorly soluble drugs. The process as disclosed combines at least one

active ingredient with at least one solubilizing agent at a low temperature "in the presence of forces sufficient to produce an active/solubilizer eutectic which is at least partially coated onto or in intimate contact with, particles of the active." WO '943 does not teach "applying shear forces after melting the drug and surfactant at the eutectic temperatures" as asserted by the Examiner in the Office Action mailed July 27, 2006, page 5, last paragraph, and certainly does not teach or suggest heating the mixture until a "clear solution" is formed. Although it is true that the reference teaches the use of "forces" there is no teaching of the use of the force on the melted clear solution.

Additionally, with regard to the present claim requirement that a "clear mixture" be formed the Examiner has stated "[a] review of the specification on pages (20 lines 1-5) and 22-23 reveals that while a clear mixture results in micro and non-crystals claimed, it is also stated that sometimes the inventive methods also results in the formation of solid." The Examiner seems to be asserting that the element of claim 18 requiring that a clear mixture of drug and surfactant be formed is meaningless. Applicants strongly disagree with such assertion. When the method of the present invention is performed as claimed to make micro- and nano-particulate drug the molten eutectic mixture formed will be clear. (Page 20, lines 1-5). The test to see if the method will work to achieve the desired micro- and nano-particulate crystals is whether or not the solution is clear. When the solution is not clear, the desired outcome of micro- and nano-particulate crystals is not achieved. Additionally, the fact that the inventive product can result in the formation of a solid is not relevant as to whether or not a clear solution needs to be achieved. The clear solution requirement applies to the drug-surfactant molten eutectic solution not to the end product. Applicants would like to emphasize that such a teaching, namely the formation of a clear solution of molten drug with a miscible surfactant, is not in the reference and believe that the Examiner may have not fully appreciated this point.

In fact, the cited reference repeatedly teaches away from the formation of such a clear molten drug-miscible surfactant solution. Before specific examples of such teaching away are set forth, the Applicants would like to summarize the current case law regarding teaching away. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material

respect." *In re Petersen*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a *prima facie* case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001) (emphasis added). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added).

Applicants assert that the presently cited reference clearly teaches away from the present invention.

One such example of such teaching away can be found on page 4, lines 11-16 of WO '943 which reads:

> If the blend of ingredients is heated too far above the point at which the eutectic alloy forms, however, it is believed that crystals of the active ingredient dissolve in the solubilizer, or melt, resulting in a saturated or even super saturated solution. Upon cooling the dissolved or melted active will then re-crystallize into crystals which are too large to benefit from improved wetting of the solubilizer/eutectic coating and not dissolve as readily. (emphasis added)

In essence WO '943 teaches that if the drug is melted or dissolved in the solubilizer (or in the present case the surfactant) the purpose of the whole process is defeated, namely the enhanced solubility benefits are destroyed. It is important to note that in the above passage, the term "melt" is used as a synonymously with "dissolve in the solubilizer." The present invention not only allows for the drug to dissolve or melt in the surfactant but it is a required element. As discussed above, the presently pending claims require that the molten surfactant be miscible with the drug, or in other words, when the drug is melted into the molten surfactant the two liquids dissolve in one another.

The undesirability of dissolving the drug in the surfactant (solubilizer) again taught in WO'943 in the specification on page 5, lines 25-30 which reads:

> In addition, it is preferable that there be sufficient "head room" between the solubilizer melt temperature and the active melt temperature to enable one to process the combination at a temperature sufficiently low such that the active does not dissolve [melt] in the solubilizer. It is believed that if too much of the active ingredient dissolves in the eutectic, upon cooling the active will form crystals which will be so large that the cannot benefit from the wetting effects of the solubilizer and therefore, not dissolve as readily. (Emphasis added)

This idea is again reiterated on page 6, lines 20-25 which reads:

> Preferably the temperatures at which the ingredients are contacted are below the formation point of the combination's eutectic to below the temperature at which the active will dissolve in the solubilizer so that the drug does not totally dissolve [melt] in the eutectic. When temperatures are too high, one or both of the ingredients can, upon cooling crystallize too quickly, resulting crystal reformation which are too large to take advantage of the wetting properties of the solubilizer/eutectic.

Based on the above listed passages, it is clear that not only does WO' 943 fail to teach each and every element of the currently pending claims, namely melting the drug in the surfactant, it also repeatedly teaches away from such a method. As set forth above, the Federal Circuit has held that when a reference teaches away from an invention it cannot serve as a *prima facie* case of obviousness.

In addition, the presently pending claims require that the drug surfactant mixture be heated to a temperature which is higher than the temperature levels taught in WO '943. The Examiner has asserted that the temperature ranges taught in WO '943, ("processed at low temperatures, i.e. temperatures below the melting points of both, and preferably from below the formation temperature of a eutectic of the active and solubilizer combination to below the temperature at which the active dissolves" (*See*, page 2 lines 21-21)) is sufficient to render obvious all temperatures which are above the mixture's melting point but below the decomposition temperature of the drug. The Applicants respectfully submit that such an assertion is incorrect.

The Applicants previously noted that the specification of WO '943 gives further limitation to the upper temperature range for use in its invention. On page 6, lines 26-28 the specification states:

> Typical temperatures used in the invention range from at or below the standard eutectic formation temperature to **below** the temperature at which the active melts or readily dissolves in the solubilizer. (emphasis added)

In response to this the Examiner stated that it is not persuasive "because the teachings of the prior art are not limited to preferred embodiments and instead should be considered as a whole…." (Office action dated 7/27/06, page 8). The Applicants assert that the above limitation is not merely a preferred embodiment, but rather is a limitation on the taught temperature range. Such an assertion is supported when, as the Examiner has argued, the reference is "considered as a whole." Consideration of WO'943 as a whole results in temperature ranges which are "sufficiently low such that the active does not dissolve [melt] in the solubilizer," which have low enough "so that the drug does not totally dissolve [melt] in the eutectic," and which are "below the temperature at which the active melts or readily dissolves in the solubilizer." As set forth above, WO'493 teaches that when the temperature is above these limits "one or both of the ingredients can, upon cooling crystallize too quickly, resulting crystal reformation which are too large to take advantage of the wetting properties of the solubilizer/eutectic." In other words temperature ranges above the limits render the invention of WO'943 inoperable.

In essence, when considered as a whole, the specification of WO'943 clearly limits the temperature range to a range lower than required in the presently pending claims, namely a temperature sufficient to melt the drug in the surfactant. This requirement inherently requires that the temperature of the process be at a high enough temperature to melt the drug, something that WO '943 expressly excludes or prohibits (see teaching away discussion above). By requiring the melting of the drug into the surfactant, the present invention goes directly contrary to the teachings of WO '943, or in other words, WO '943 teaches away from the use of temperatures high enough to melt the drug.

As WO '943 fails to provide any motivation or suggestion to be modified in a manner that would teach or suggest the present invention, and in fact, repeatedly teaches away from the claimed method. As such the Applicants respectfully submit that WO'943 does not render the present invention obvious and does not constitute a *prima facie* case of obviousness. Therefore, it is respectfully requested that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that pending claims 18, 20, 22-28, 30-36, and 38 present allowable subject matter and allowance thereof is respectfully requested. If any impediment to the allowance of these claims remains after consideration of the above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

Please charge any additional fees except for Issue Fee or credit any overpayment to Deposit Account No. 20-0100.

Dated this 30th day of September, 2006.

Respectfully submitted,

/David W. Osborne/

David W. Osborne

Attorney for Applicant
Registration No. 44,989

Of:

THORPE NORTH & WESTERN, LLP
8180 South 700 East, Suite 200
Sandy, Utah 84070
(801) 566-6633